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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/772,272 | TOMINAGA ET AL. | |
| | Examiner | Art Unit | |
| | Vanessa L. Ford | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) *9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**FINAL ACTION**

1. This action is responsive to Applicant's amendment and response filed August 4, 2006. Claims 1 and 3-6 have been amended. Claims 2 and 8 have been cancelled. Claims 11-12 have been added. Claims 9-10 and newly submitted claims 11-12 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

***Rejections Withdrawn***

3 In view of Applicant's amendment and response the following rejections are withdrawn:

a) rejection of claims 1-8 under 35 U.S.C. 102(b), pages 6-8, paragraph 3 of the previous Office action.

b) rejection of claims 1-8 under 35 U.S.C. 102(b), pages 8-10, paragraph 4 of the previous Office action.

c) rejection of claims 1-8 under 35 U.S.C. 102(b), pages 10-11, paragraph 5 of the previous Office action.

***Rejections Maintained***

4. The rejection under 35 U.S.C. 112, first paragraph is maintained for claims 1, 3-7 for the reasons set forth on pages 3-6, paragraph 2 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a *Bacillus* bacterium which is modified so that growth inhibition by 6-ethoxypurine is reduced and has inosine-producing ability.

The claims broadly encompass a genus of *Bacillus* mutants. There is substantial variability among the species of *Bacillus* mutants encompassed within the scope of the claims. The instant specification teaches that *Bacillus* mutants of the invention can be made by mutagenesis treatment with UV irradiation or treatment with mutagenizing agent used for typical mutagenesis treatment such as N-methyl-N'-nitro-N-nitrosoguanidine (NTG) and nitrous acid (page 13). The specification teaches that mutations may be made by disruption of the "normal gene" with a "disrupted-type purR gene" (pages 8-9). The instant specification teaches that the disrupted-type purR gene can be obtained by specifically using deletion of a certain region of the purR gene using digestion with restriction enzyme and re-ligation, insertion of another DNA fragment (marker gene etc.) into the purR gene (site-directed mutagenesis). The specification does not place any structure limitations on the *Bacillus* mutants. The instant specification does not teach what locations in the purR gene are mutated to arrive at the claimed *Bacillus* bacterium. The scope of the claims include numerous structural variants and the genus is highly variant because a significant number of structural difference between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the gene class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. There is no guidance provided as to which nucleic acids can be deleted or substituted and the encode polypeptide still has its biological function. Since the purR nucleic acid sequence encodes a protein, the prior art below teaches the difficulties associated with amino acid modification within a protein.

*Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (pages 314-315)* teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort

the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain have no great effect on stability.

Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach, 1989; pages 184-186*" teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented. The mere recitation of a "...which is deficient in one or more genes negatively acting on the biosynthesis of inosine or involved in degradation of inosine and selected from a purine operon repressor gene, succinyl-AMP synthase gene and purine nucleoside phosphorylase gene" does not provide a structure for the claimed *Bacillus* mutants. One skilled in the art would not recognize from the claimed disclosure that the applicant has taught how to make and use the claimed *Bacillus* mutants. What position within the purR gene or other genes can be modified to arrive at the claimed bacterium? The specification does not enable numerous *Bacillus* mutants encompassed by the claimed invention. Therefore Applicant have not met the enablement requirements as set forth in U.S.C. 112, first paragraph.

Applicant's Arguments

Applicant urges that the basis of the rejection is faulty because no biological function is trying to be maintained. Applicant urges that modifications to a gene or protein sequence are unpredictable with regard to structure and function do not apply to the instant claims since deletion of a target gene sequence is well within the skill in the art.

Examiner's Response to Applicant's Arguments

The Examiner disagrees with the assertion that "the instant claims have no biological function". It is the Examiner's position that the claimed bacterium has the

biological function of producing inosine. Although it is well within the skill in the art to modify genes or proteins, the instant specification does not provide the guidance necessary for one of skill in the art to obtain an inosine producing bacterium since the art is unpredictable regarding gene and/or protein modification. The instant specification has not provide any guidance as to where (at what location) the "purR gene", purA gene or deoD gene are modified to result in an inosine producing bacterium. Without this guidance experimentation is undue.

In view of all of the above, this rejection is maintained since Applicant has not met their burden under 35 U.S.C. 112, first paragraph.

***New Grounds of Rejection Necessitated by Amendment***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 1 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "reduced growth inhibition by 6-ethoxypurine". It is unclear as to what Applicant intends. Does the addition of 6-ethoxypurine reduce growth or does the inosine producing bacterium process this characteristic. Correction and/or clarification is required.

6. Claim 3 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 (depends from claim 1) and claim 3 recites "ethoxypurine" is this the same as "6-ethoxypurine" recited in claim 1? Correction and/or clarification is required.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1 and 3-7 are rejected under 35 U.S.C. 102(b) as anticipated by Sato et al *(U. S. Patent No. 6,284, 495 B1 published September 4, 2001).*

Claims 1 and 3-7 are drawn to an isolated inosine-producing *Bacillus* bacterium which has reduced growth inhibition by 6-ethoxypurine as compared to Bacillus 168 Marburg strain wherein said bacterium is deficient in a gene selected from the group consisting of the purR gene, the purA gene, the deoD gene and combinations thereof.

Sato et al teach a bacterium that has been disrupted in the purR gene (see the Abstract and column 4). Sato et al teach that the bacterium of the invention was a Bacillus subtilis 168 Marburg strain (column 4). Sato et al teach that the bacterium can be used to produce nucleic acid substances including "inosinic acid". Therefore, the art teaches the claim limitation "inosine producing". Claims limitations such as " ...wherein

said reduced growth inhibition occurs in the presence of 2000 mg/L ethoxypurine" and "...wherein said reduced growth inhibition occurs on solid medium" would be inherent in bacterium of the prior art. Claims limitations such as "wherein the medium has an ethoxypurine content of 2000 mg/L", "wherein the bacterium is cultured on a solid medium containing 6-ethoxypurine and a solid medium not containing 6-ethoxypurine, the bacterium shows a relative growth degree of 80 or more which is defined by the following equation: Relative growth degree (%) =[colony diameter (mm) observed in the medium containing 6-ethoxypurine]/[colony diameter (mm) observed in the medium not containing 6-ethoxypurine] x 100", "wherein the solid medium containing 6-ethoxypurine comprises 6-ethoxypurine content of 2000 mg/l.", "wherein the solid medium is a minimal medium" and "which is deficient in one or more genes negatively acting on the biosynthesis of inosine or involved in degradation of inosine and selected form a purine operon repressor gene, succinyl-AMP synthase gene and purine nucleoside phosphorylase gene" are being viewed as process limitations. It should be noted that the products of the prior art reference appear to be the same or an obvious or analogous variant of the product claimed by the applicant because they appear to possess the same or similar functional characteristics. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). Even if applicant's

product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity is relied upon.

Since the Office does not have the facilities for examining and comparing applicant's bacterium with the bacterium of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the bacterium of the prior art does not possess the same material structural and functional characteristics of the claimed bacterium). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

***Status of Claims***

8. No claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

***Conclusion***

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Albert Navarro, can be reached at (571) 272-0861.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
October 7, 2006

NITA MINNIFIELD
PRIMARY EXAMINER